Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-26 are pending in the application, with claims 1, 12, and 13 being the independent claims. Claims 20, 22, 24, and 26 are withdrawn from further consideration. Claims 1, 12, and 13 are amended. Support for the amendment to claim 1 is found in paragraphs 32 (pages 15-16), 33 (page 16), and 37 (page 17) of the specification. Support for amendment to claims 12 and 13 is found in paragraphs 32 (page 15-16) and 33 (page 16) of the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim Objections

The Examiner objected to claim 12 over the parenthesis around the term "Yersinia pestis." Applicants disagree with the objection.

To expedite the prosecution of the application, applicants deleted the term "Yersinia pestis" from claim 12. Reconsideration and withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 112

(i) First Rejection

The Examiner rejected claims 1-3, 5-19, 21, 23, and 25 under 35 U.S.C. § 112, first paragraph, allegedly because

> the specification while providing enablement for showing an improvement in survival rate of mice by the administration of an intravenous injection of a caspase inhibitor, Cbz-Val-Asp-Ch_2F [sic], after what was established by Applicant as a lethal dose of ^{137}Cs does not reasonably provide enablement for protecting against chemical and biological exposure, does not provide support for an effective dosage administration route, has not shown the caspase inhibitor to be effective when administered prior or during an exposure event and has not shown unintentional exposure from a nuclear plant, research facility, etc. or intentional exposure from a bomb or a spill. Furthermore, Applicant has not reasonably provided support for the only compound tested on the mice, Cbz-Val-Asp-Ch_2F, works via the mechanism of action for which Applicant purports, reduction in cell death, specifically in the gastrointestinal tract, skin, hair, bone marrow, immune system, nervous system or liver.

Office Action ("OA"), page 4. Further, the Examiner alleges that "Applicant has failed to elucidate if the compound is working via the mechanism of action which Applicant claims." *Id.*, page 7. Applicants traverse this rejection.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971) (emphasis in original). There is no scientific evidence for the Examiner's assertion that "showing an improvement in survival rate of mice by the administration of an intravenous injection of a caspase inhibitor, Cbz-Val-Asp-Ch_2F" does not "reasonably provide[] support for the only compound tested on the mice, Cbz-Val-Asp-Ch_2F, works

via the mechanism of action for which Applicant purports, reduction in cell death."

OA, page 4.

According to the specification,

> Radiation is known to cause apoptotic cell death (Paris *et al.*, *Science 293*:293-7 (2001) and Sheikh *et al.*, *Oncogene 17*:2555-2563 (1998)). The present invention arises out of the discovery that caspase inhibitors, which can inhibit apoptosis, are useful for the treatment of radionuclide-induced cell death. Therefore, this invention is useful for the treatment of diseases and conditions, including death, caused by exposure to radionuclides, spread of radionuclides, so called "dirty bombs" exploded by terrorists, or accidental exposure to radionuclides from nuclear power plants, nuclear research facilities or hospitals. Furthermore, this invention is useful for the protection of cells surrounding a treatment site during treatment of cancer or other conditions with radiopharmaceutical agents and the protection of cells during administration of radiolabeled imaging agents. These types of radionuclide exposure are distinguished from therapeutic radiation treatment, as exemplified by radiation therapy for cancer.

Specification, paragraph 31. The Examiner did not provide any evidence that radiation does not cause apoptotic cell death. Further, the Examiner did not provide any evidence to counter Applicants' contention that caspase inhibitors such as Cbz-Val-Asp-CH_2F would inhibit apoptosis induced by radiation. Without any specific evidence to support Examiner's contentions, Examiner's assertions are legally insufficient to establish *a prima facie* case of lack of enablement. Accordingly, applicants respectfully request that this aspect of the rejection be withdrawn.

Further, the Examiner asserts that the specification "does not reasonably provide enablement for protecting against chemical and biological exposure." OA, page 4. In particular, the Examiner alleges that "the assertion of the ability to inhibit cell death during a chemical agent or biological agent exposure event, without actually conducting

testing or referencing prior art to the fact of the compounds of interest, makes practicing the invention unpredictable." OA, page 7.

In order to expedite the prosecution of the application, Applicants amended claim1 such that the recited chemical and biological agents are limited to those known to cause cell death via apoptosis as specifically described in the specification. The specification discloses that

> [m]any biological agents, such as those pathogens and toxins that have been used to make biological weapons, including anthrax (Park *et al.*, *Science 297*:2048-2051 (2002) and Popov *et al.*, *FEBS Lett. 527*:211-215 (2002)), botulinum (Rohrbach *et al.*, *Ann. Otol. Rhinol. Laryngol. 110*:1045-1050 (2001) and Doggweiler *et al.*, *Prostate 37*:44-50 (1998)), aflatoxin (Sun *et al.*, *Biomed. Environ. Sci. 15*:145-152 (2002) and Meki *et al.*, *Neuroendocrinol. Lett. 22*:417-426 (2001)), Clostridium (Brito *et al.*, *J. Infect. Dis. 186*:1438-1447 (2002) and Qa'Dan *et al.*, *Cell. Microbiol. 4*:425-434 (2002)), plague (*Yersinia pestis*) (Weeks *et al.*, *Microb. Pathol. 32*:227-237 (2002), Cornelis, *Proc. Natl. Acad. Sci. USA 97*:8778-8783 (2000) and Mills *et al.*, *Proc. Natl. Acad. Sci. USA 94*:12638-12643 (1997)), hemorrhagic fevers (Ebola and Marburg) (Baize *et al.*, *Apoptosis 5*:5-7 (2000), Geisbert *et al.*, *Lab. Invest. 80*:171-186 (2000) and Baize *et al.*, *Nature Med. 5*:423-426 (1999)), Staphylococcus (Mempel *et al.*, *Br. J. Dermatol. 146*:943-951 (2002) and Kerro *et al.*, *Vet. Q. 24*:181-198 (2002)), Streptococcus (Kemp *et al.*, *Infect. Immun. 70*:5019-5025 (2002) and Buratta *et al.*, *FEBS Lett. 520*:68-72 (2002)), ricin, modeccin, diphtheria, and Pseudomonas (Gan *et al.*, *Acta Pharmacol. Sin. 21*:243-248 (2000), Hasegawa *et al.*, *Biosci. Biotechnol. Biochem. 64*:1422-1429 (2000) and Komatuu, *J. Biochem. (Tokyo) 124*:1038-1044 (1998)), and cholera (Pitman *et al.*, *Biochem. Soc. Trans. 26*:S338 (1998) and Allam *et al.*, *Cancer Res. 57*:2615-2618 (1997)), are known to induce apoptosis in cells. Therefore, caspase inhibitors, which can inhibit apoptosis, are useful for the treatment of cell death induced by biological agents, including those mentioned herein above. This invention is useful for the treatment of diseases and conditions, including death, caused by exposure to biological agents, including spread of biological agents by terrorists or accidental exposure to biological agents from manufacturing or processing plants, research facilities, or hospitals.
>
> Many chemical agents, such as those that have been used to make chemical weapons, including nitrogen mustard (Cai *et al.*,

> *Mol. Cancer Ther. 1*:21-28 (2001), Ardelt *et al.*, *Int. J. Oncol. 18*:849-853 (2001) and Pette *et al.*, *Immunopharmacology 30*:59-69 (1995), and cyanide (Li *et al.*, *Toxicol. Appl. Pharmacol. 185*:55-63 (200) and Prabhakaran *et al.*, *J. Pharmacol. Exp. Ther. 303*:510-519 (2002)), are known to induce apoptosis in cells. Therefore, caspase inhibitors, which can inhibit apoptosis, are useful for the treatment of cell induced by chemical agents, including those mentioned herein above. This invention is useful for the treatment of diseases and conditions, including death, caused by exposure to chemical agents, including spread of chemical agents by terrorists or accidental exposure to chemical agents from manufacturing or processing plants, research facilities, or hospitals.

Specification, paragraphs 32 and 33. The Examiner did not provide any evidence that chemical and biological agents recited in amended claim 1 do not cause apoptotic cell death. Further, the Examiner did not provide any evidence to counter Applicants' contention that caspase inhibitors such as Cbz-Val-Asp-CH_2F would inhibit apoptosis induced by the chemical and biological agents recited in claim 1. Without any specific evidence to support Examiner's contentions, Examiner's assertion that the specification "does not reasonably provide enablement for protecting against chemical and biological exposure" is legally insufficient to establish *a prima facie* case of lack of enablement. Accordingly, applicants respectfully request that this aspect of the rejection be withdrawn.

The Examiner further alleges that "it is impossible to predict if administration prior or during an exposure event would be capable of having an effect, due to unknown clearance rates of compounds in the subject." OA, page 7. Applicants disagree.

The Examiner appears to require that Applicants determine all the parameters necessary for the invention to be marketed. However, that is not necessary to satisfy the enablement requirement. For the enablement requirement to be satisfied, it is sufficient

to provide sufficient guidance for a person skilled in the art to practice the invention. Applicants assert that a skilled artisan would be able to optimize both the dosage and timing of the administration using the disclosure of the application. Moreover, Applicants provided an example which shows that administration of the caspase inhibitor immediately after gamma radiation is effective to treat or ameliorate cell death induced by gamma radiation. Further, there is no reason to believe that administering the caspase inhibitor before or simultaneously with the gamma radiation would make the drug ineffective. Applicants therefore respectfully request that this aspect of the rejection be withdrawn.

The Examiner further alleges that "without actually determining if oral or topical administration is actually effective through prior art or applicant's own work, it would be unpredictable if compound would be effective at treating an exposure event." OA, page 7. Applicants disagree.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original).

In support of this basis for rejection, the Examiner appears to doubt the effectiveness of oral and topical administration of the drug without providing any reason

except to state that it is unpredictable. Without any specific support, such assertions are legally insufficient to establish *a prima facie* case of lack of enablement. In the absence of any such specific evidence showing that the specification is not enabling for the claimed invention, the invention must be considered to be enabled. Accordingly, applicants respectfully request that this aspect of the rejection be withdrawn.

The Examiner also alleged that the specification "has not shown caspase inhibitor [Cbz-Val-Asp-CH_2F] to be effective . . . [after] unintentional exposure from a nuclear power plant, research facility, etc. or intentional exposure from a bomb or a spill." OA, page 4. Applicants disagree.

Applicants note that whether a caspase inhibitor Cbz-Val-Asp-CH_2F would inhibit apoptosis induced by radiation is not relevant to whether the exposure is intentional (e.g., detonation of a dirty bomb) or unintentional (e.g., accidental release from a power plant). The Examiner has not provided any evidence or sound scientific reasoning why the effectiveness of a caspase inhibitor Cbz-Val-Asp-CH_2F to inhibit apoptosis induced by radiation would be compromised based on the intent of the person or entity that caused the release of the radiation. Without any specific support, Examiner's assertions are legally insufficient to establish *a prima facie* case of lack of enablement. In the absence of any such specific evidence or sound scientific reasoning why the specification is not enabling for the claimed invention, the invention must be considered to be enabled. Accordingly, applicants respectfully request that this aspect of the rejection be withdrawn.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5-19, 21, 23, and 25 under 35 U.S.C. § 112, first paragraph.

(ii) Second Rejection

The Examiner also rejected claims 1-19, 21, 23, and 25 under 35 U.S.C. § 112, first paragraph, allegedly because "[t]he use of the terminology 'of preventing' in the first line of claim 1 is contentious." OA, page 10. According to the Examiner, "nowhere in the art or instant application has the efficacy of the caspase inhibitor, Cbz-Val-Asp-CH_2F, been enabled to prevent or completely control apoptosis and subsequent death of the subject." *Id.* Applicants traverse this rejection.

To expedite the prosecution of the application, Applicants deleted the term "preventing" from claim 1. Claims 2-19, 21, 23, and 25 depend directly or indirectly from claim 1. Therefore, none of claims 1-19, 21, 23, and 25 refers to the contested term. Accordingly, reconsideration and withdrawal of the rejection of claims 1-19, 21, 23, and 25 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-5, 8, and 14-19 under 35 U.S.C. §102(e) as being anticipated by WO 01/27140 ("Weber"). Office action, page 11. According to the Examiner,

> Weber et al teaches the use of a caspase inhibitor to treat, ameliorate or prevent bone marrow cell death in an animal via administering a caspase inhibitor (Claim 1). Weber et al teaches topical or oral administration (claim 2) or injection (claim 11) and a pharmaceutical composition with an acceptable carrier (claim 12). Weber et al teaches the intentional administration due to chemotherapy (claim 1). Weber et al teaches the administration of the caspase inhibitor prior, during or after the exposure event (claims 17-19). Weber et al teaches various caspase inhibitor compounds (claims 13-16) which includes the compound Cbz-Val-Asp-CH_2F (claim 14, line 3).

Id. Applicants traverse this rejection.

Solely to expedite the prosecution of the application, Applicants amended claim 1 such that the recited radionuclide is not a measured dose of radiation for cancer therapy. Support for this amendment may be found at paragraph 37 of the application where the specification states "[t]hese types of exposure are distinguished from exposure of patients to measured doses of radiation for therapeutic reasons, such as radiation treatment of cancer." Because Weber does not teach use of caspase inhibitors to treat apoptotic cell death caused by radiations that are not exposed to the animal for therapeutic purposes, it does not anticipate any of the claims of the present invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Bashir M.S. Ali
Attorney for Applicants
Registration No. 47,939

Date: March 19, 2008

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
766653_1.DOC